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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,029	07/25/2005	Zita Jegesne Csakai	CytRx/016	3625

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EXAMINER	
HABTE, KAHSAY	
ART UNIT	**PAPER NUMBER**
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,029	CSAKAI ET AL.	
	Examiner	Art Unit	
	Kahsay Habte	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-36* is/are pending in the application.

4a) Of the above claim(s) *22-26,33 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35 and 36* is/are rejected.

7)☒ Claim(s) *21 and 27-32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 21-36 are pending in this application.

Election/Restriction

2. Applicant's election with traverse of Group I filed 3/12/2007 is acknowledged. The traversal is on the ground(s) that "the inventions are not independent. Compounds of formula III are actually subspecies of formula I. Namely, when X of formula I is NR^4R^5, and R^4 is a hydrogen and R5 is branched C_{1-6} alkyl group, and Y is a hydrogen, with R^5 being part of the cyclic structure in formula (III)." The examiner disagrees with applicant's argument. Groups I-II are independent one from the other because each group's compounds are made and used independently of each other and could support separate patents. Note that Groups I-II are directed to structurally dissimilar compounds such that the variable core created by the varying definitions of variables in formulae **I-III** do not belong to the same recognized class of chemical compounds in the art, and references anticipating one invention, would not render obvious the others. Group I is drawn to 1,2,4-oxadiazines (six-membered ring with an oxygen and two nitrogens) and is different from Group II that is drawn to others e.g. pyridines, morpholines, etc. Thus, separate searches in the literature as well as in the U.S. Patent Classification System would be required. The compounds differ significantly in chemical structures. One skilled in the art would not consider such diverse structure equivalents of each other. Coexamination of the additional group would require search of subclasses unnecessary for the examination of the elected claims. For example, the

search for the invention of Group II would include search of classes 544, 546, 564 and various subclasses. Therefore, coexamination of the additional invention would require a serious additional burden of search.

The requirement is still deemed proper and is therefore made FINAL.

Claims 22-26 and 33-34 are withdrawn from prosecution as being drawn to non-elected invention.

3. The claims are drawn to multiple inventions for reasons set forth in the restriction requirement. The claims are examined only to the extent that they read on the elected invention. Cancellation of the non-elected subject matter is recommended in response to this Office Action.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In claim 36, it is recited a method for the treatment or prevention of vascular disease or

diseases related to vascular disorders, but the specification is not enabled for such a scope.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The scope of the claims is not adequately enabled solely based on the vaso-relaxing effect activity provided in the specification. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as pharmaceutical effective hydroxylamine derivatives, which are useful in the treatment of vascular diseases. Test procedures and assays are provided in the specification at pages 8-13 only for 6 compounds and it is concluded that the test compounds improved the relaxation properties significantly, which is the result of the functioning of the endothelium, due to the relative increase of the endothelium-related relation factors. However, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders embraced the instant claims. The disorders encompassed by the instant claims (i.e. treatment of vascular diseases), some of which have been proven to be extremely difficult to treat. Vascular diseases are very broad in

nature and differ one from the other significantly. Vascular disease is mainly caused by atherosclerosis (hardening of the arteries) due to a thickening of the lining of the arteries. The arteries are blood vessels that supply blood, oxygen and nutrients, to the body from the heart. Atherosclerosis is a condition leading to narrow, hardened arteries so that there is insufficient blood flow to satisfy the needs of the tissue in question. Those parts of the body most affected by this disease suffer the consequences of an inadequate blood supply, namely poor function, tissue damage or death. There are different symptoms depending on where in the body the vascular disease occurs. It most commonly affects the arteries of the heart, brain and legs.

The heart - cardiovascular disease

When the heart is affected, heavy, tight central chest pain with exertion (angina) or breathing difficulties may be experienced. In the most serious cases, a coronary artery can become blocked by a blood clot (thrombosis) causing severe pain and a serious threat to life.

Cardiovascular disorders embrace a vast array of problems, many of which are contradictory to others. Thus, it covers hypertension and hypotension. It covers various types of arrhythmias; angina pectoris; the thrombotic symptoms of diabetes, atherosclerosis and hyperlipoproteinaemias; ischaemic heart disease including congestive heart failure and myocardial infarction; stroke, and peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis percutaneous transluminal coronary angiography (PTCA); elevated blood levels of triglycerides, of

total cholesterol or of LDL cholesterol; arteriosclerosis, peripheral vascular disease, cerebral vascular disease and pulmonary hypertension, migraine, cardiomyopathy, etc. Not one compound --- let alone a genus of trillions of compounds, could possibly be effective against such disorders generally.

The brain - cerebrovascular disease

Atherosclerosis in the arteries of the brain can lead to strokes (CVAs) that cause paralysis or loss of other function, such as speech.

The legs - peripheral vascular disease

In the legs, atherosclerosis may cause cramping pain in the muscles on exertion (intermittent claudication).

There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the

unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

In regard to the prevention of vascular diseases in general, to this day the only thing available is the treatment of some type of vascular diseases, but not preventing someone from getting vascular disease in the first place.

It is recommended that applicants delete claim 36 to overcome this rejection.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a. Claim 35 is rejected because the pharmaceutical composition lacks a carrier.

b. In claim 36, the phrase "diseases related to vascular disorders" is indefinite. What is covered and what is not?

Specification

6. The specification is objected to because of the term "Dragées" at page 23, line 8 and the phrase "dragée cores" at page 23 (line 24) appears to be foreign terminology. It is recommended that applicants amend the specification to fix said term or other terms if present in the specification.

7. The specification is objected to because it is unclear what the term "q. s. ad." at pages 24-25 stands for. It is also unclear what "pyrogen-free" at pages 24-25 is. It is recommended that applicants review the specification and correct the specification for typographical errors.

Objection

8. Claims 21,and 27-32 are objected to and would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (571) 272-0661. The fax phone

number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kahsay Habte
Primary Examiner
Art Unit 1624

KH
March 27, 2007